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McCtreen, Doyle, Brown & Enersen, LLP – (415) 393-2000

Invertible: Chemically Modified Mutant Serine Hydrolases Show Improved Catalytic Activity and Chiral Selectivity

Fig. 1

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Invent John Bryan Jones, et al.

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Scheme 1. Modification of SBL mutants with Chiral Auxiliaries.

$$R = S \xrightarrow{QR^{1}} (R)-a R^{1} = Me$$

$$(R)-b R^{1} = H$$

$$R = S \xrightarrow{QR^{1}} C R^{1} = H$$

$$(R)-b R^{1} = H$$

$$R = S \xrightarrow{QR^{1}} C R^{1} = H$$

$$(R)-d R^{1} = iPr$$

$$(R)-e R^{1} = Pr$$

$$(R)-f R^{1} = Br$$

$$R = S$$
 $(R)-g$
 $R^1 = Ph$
 $(R)-h$
 $R = S$
 $(R)-i$

The corresponding (S) MTS ligands follow the same code scheme (i.e. (S)-a, (S)-b, (S)-d, (S)-e, (S)-f, (Ś)-g, (S)-h, (S)-i).

Fig. 2

Scheme 2. Synthesis of Mandelate-based Ligands

OR OR OR OR (iv) OR (viii) OR SSO₂CH₃

(i)
$$(R)$$
-2 R = H, R¹ = H (ii) (v) (R)-6 R = Me, R¹ = OH (viii) (R)-12 R = MOM (R)-12 R = MOM (R)-7 R = MOM, R¹ = OH (R)-1b R = H (R)-8 R = Me, R¹ = OSO₂CH₃

(iii) (R) -5 R = MOM, R¹ = Me (vi) (R)-9 R = MOM, R¹ = OSO₂CH₃

(R)-10 R = Me, R¹ = Br

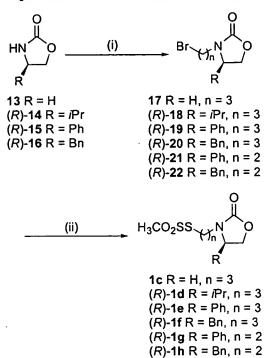
(R)-11 R = MOM, R¹ = Br

Reagents: (i) Me₂SO₄, NaOH, H₂O, 37%; (ii) MeOH, H⁺; (iii) MOM-Cl, CH₂Cl₂, Et₃N (90% 2 steps); (iv) For (R)-3: BH₃, THF, 82%; For (R)-5: LiBH₄, THF, 97%; (v) MeSO₂Cl, CH₂Cl₂, Et₃N; For (R)-8: 100%; (vi) LiBr, acetone; For (R)-10: 84%; For (R)-11: 78% 2 steps; (vii) NaSSO₂CH₃, DMF; For (R)-12: 61%; (viii) TFA, H₂O, 82%.

Fig. 3

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Scheme 3. Synthesis of Oxazolidinone-based Ligands



Reagents: (i) KOH, DMSO, Br (CH₂)_nBr; (ii) NaSSo₂CH₃, DMF.

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Scheme 4. Synthesis of Indanol-based Ligands

H₂N OH
$$(R)-23$$

$$(R)-24$$

$$(R)-25 R = Br$$

$$(R)-11 R = SSO2CH3$$

Reagents: (i) triphosgene, CH_2CI_2 , Et_3N , 100%; (ii) KOH, DMSO, $Br(CH_2)_3Br$; (iii) $NaSSO_2CH_3$, DMF.

Fig. 5

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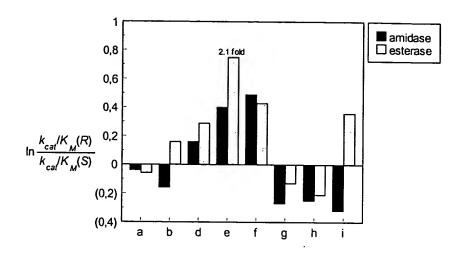
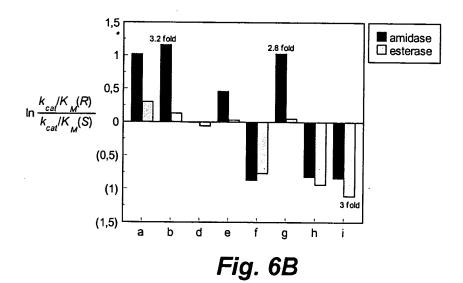


Fig. 6A



APPRICE D.G. F. 3.

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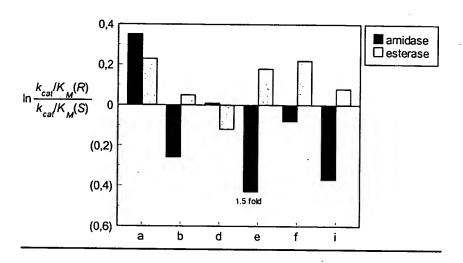


Fig. 6C